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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,450	12/30/2003	Richard L. Boyd	286336.150US1/NOR-011CP2	2366

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12/15/2006

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EXAMINER

BELYAVSKYI, MICHAEL A

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/748,450

Applicant(s)

BOYD, RICHARD L.

Examiner

Michail A. Belyavskiy

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 October 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 15-23, 25-33, 35-68 and 72-76 is/are pending in the application.
- 4a) Of the above claim(s) 16-23, 25-29, 37, 38 and 72 - 74 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15, 30-33, 35, 36, 39-60, 63-68, 75 and 76 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 10/13/06.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- ☐ Notice of Informal Patent Application
- ☐ Other: _____.

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RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 10/13/06 is acknowledged.

Claims 15-23, 25-33, 35-68 and 72-76 are pending.

2. Claims 16-23, 25-29, 37, 38 and 72 - 74 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

3. *Claims 15, 30-33, 35, 36, 39-60, 63-68, 75 and 76 drawn to a method for improving an immune response to a vaccine antigen in a patient, wherein the method of disrupting sex steroid mediated signaling to the thymus is through administration of one or more pharmaceutical, wherein pharmaceutical are recited in claims 40, 41 and 42 and wherein vaccine antigen is recited in claim 45 and wherein vaccine is recited in claim 63 and cytokine is recited in claim 67 and growth factor is recited in claim 68 are under consideration in the instant application.*

In view of the amendment, filed 10/13/06 the following rejections remain:

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 15, 30-33, 35, 36, 39-60, 63-68, 75 and 76 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons set forth in the previous Office Action mailed on 04/10/06.

Applicant's arguments filed on 10/13/06 have been fully considered but have not been found convincing.

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Applicant asserts that : (i) There is no statutory requirement for working examples, including animal model data, for a disclosure to be enabling; (ii) Applicant has provided several prophetic examples, that provide guidance to one of ordinary skill in the art to practice the claimed invention. (iii) The Examiner misinterpreted the statement on page 103 in the Example 10, since Example 10 is a prophetic example and thus describes an embodiment of the invention based on predicted results rather than work actually conducted, thus the statement on page 103 does not indicate that the claimed method does not work in mice and/or humans; (iv) Declaration under U.S.R 1.132 by Dr. Boyd provided further evidence that the invention as claimed is fully enabled.

Contrary to Applicant's assertion, the issue raised in the previous Office Action was not about the requirement of providing animal model data or working examples. As has been stated previously, the specification only discloses data of enhanced regeneration of thymus of castrated mice. In said experiments thymus has been reactivated by removing the effects of sex steroid on the thymus after surgical castration. However, the specification disclosed that regenerated thymus maintains its functional capacity with T cell proliferation, differentiation, and increasing in thymocyte number, replenishing all T cell subpopulations and migration capacity. (see examples I- V in particular). The specification also disclosed a detailed method of delivery said pharmaceuticals into the patients (see examples VI-VIII in particular). Examples IX-XI in the instant Specification are prophetic examples that indicate what the inventor thinks might happen in the experiments which have not actually been performed. The specification does not adequately teach how to effectively improve an immune response to a vaccine antigen in a patient, comprising reactivating the thymus, claimed in claim 15, wherein reactivating is by disrupting of sex-mediated signaling to the thymus claimed in claim 30, by administration of one or more pharmaceutical, wherein pharmaceutical are recited in claims 40, 41 and 42 and wherein vaccine antigen is recited in claim 45 and wherein vaccine is recited in claim 63 and cytokine is recited in claim 67 and growth factor is recited in claim 68. Moreover, no animal models were used to study the effectiveness of the method for improving an immune response as claimed in claims 15, 30-33, 35, 36,39-60, 63-68, 75 and 76. Since there is no animal model data and studies in the specification showing the effectiveness for improving an immune response to a vaccine antigen by disrupting sex steroid mediated signaling through administering one or more pharmaceutical, it is unpredictable how to correlate *in vivo* results of regeneration of thymus by removing the effects of sex steroid on the thymus after surgical castration with claimed method for improving an immune response to a vaccine antigen by disrupting sex steroid mediated signaling through administering one or more pharmaceutical as claimed in claims 15, 30-33, 35, 36,39-60, 63-68, 75 and 76. Feldman et al. (Transplantation Proceeding, 1998, Vol.30, pages 4126-4127). teach that "while it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease, leading to interesting dilemmas such as how much can we rely on and extrapolate from animal models in disease". Feldman et al. further teach that in a chronic immune-driven inflammatory response there are a number of pathways that become

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engaged and effective therapy in immune diseases such as rheumatoid arthritis, will come from therapy aimed at several points in the disease pathway. In addition, Windmill et al., (IDS) teaches that while it is tempting to speculate that castration removes inhibitory factors on thymic hormone expression, the observation that removal of gonadal steroids results in thymic hypertrophy may not be explained by a simple relationship. It has been acknowledged that a hypothalamus-pituitary-thymic-gonadal axis operates under a series of complex pathways (see entire document, page 111 in particular). Further, Fabris et al. (IDS) also stated that finding related to neuroendocrine-immune interaction should be cautiously evaluated since stimuli required to activate a given pathway as well as the end result may be quite different, either quantitatively or qualitatively, according to the functional demand, morphogenic or of actual performance of the organism. Moreover, Applicant himself acknowledges that the precise target of the sex steroid hormones and the mechanism by which they induce thymus atrophy is yet to be determined. Thymic function is regulated by several complex interactions between the neuroendocrine-immune axes which are not fully understood. Applicant further stressed that signaling by sex steroid is the net result of complex outcomes of the components of the pathways that includes biosynthesis, secretion etc., and these pathways are not fully understood. (see page 5, lines 10-15, page 40 and overlapping pages 69-70 in particular).

Moreover, at issue is whether or not the claimed method would be efficient for improving an immune response to a vaccine antigen, by disrupting sex steroid mediated signaling through administering one or more pharmaceuticals as claimed in claims 15, 30-33, 35, 36, 39-60, 63-68, 75 and 76. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use said pharmaceutical composition and vaccine as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical composition and vaccine are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed method with a reasonable expectation of success.

The claims are drawn to a method of improving vaccinating a mammal. By definition, a vaccine is a composition to induce a specific immunity that **prevent** or protect against a specific disease caused by a specific agent. One of the criteria for a vaccine is the levels of antibody (humoral immune response) before and after immunization and the success of vaccination is judged by the extent of increase in the level of antigen-specific antibody. The second criterion for a vaccine is the ability to stimulate memory T lymphocytes (cell-mediated immune response) (See Janeway et al., Immunobiology, Third Edition, Chapter 13, pages 579-583 in particular). The specification provides no information on the immunogenicity of *any* vaccine antigen, wherein vaccine antigen is recited in claims 45-60 or the ability of such vaccine antigen to protect or prevent from antigen-specific disease. The specification fails to teach that *any* vaccine antigen, as recited in claims 45-60 are capable of generating an antibody response or cell-mediated immune response. The specification also fails to teach that the antibody response or cell-mediated immune response to the claimed *any* vaccine antigen, as recited in claims 45-60 provides for a protection against infection. Vaccines by definition trigger an immunoprotective response in the host vaccinated and mere antigenic response is insufficient. It is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a

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pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of "VACCINES" [Plotkin, S.A. et al. (eds) published by W. B. Saunders company (Philadelphia) in 1988, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack by the pathogen". Moreover, Chandrasheker et al., (US Patent 6,248,329) teach that although many investigators have tried to develop vaccines based on specific antigens, it is well understood that the ability of an antigen to stimulate antibody production does not necessarily correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from specific disease, associated with said antigen (see column 1, lines 35-45 in particular). In addition, Spitler, (Cancer Biotherapy, 1995, v.10 pages 1-3 teaches that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company, and you're likely to get the same response" (see page 1, column 1, paragraph 1 in particular). The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. Ezzell (NIH Research, 1995, Vol.7, pages 46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see entire document, particularly the last paragraph). It is well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; page 48, column 2, paragraph 2). Furthermore, no one is very optimistic that a single peptide or a virus carrying the gene encoding that peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (Ezzell; page 48, paragraph 6).

With regards to Applicant's statement that the Examiner misinterpreted the statement on page 103 in the Example 10.

The Examiner does not indicated that the claimed method does not work in mice and/or humans as alleged by Applicant. The Examiner only stated, that, since Example 10 is a prophetic example and thus describes an embodiment of the invention based on prophetic results that Applicant think he might obtain rather than work actually conducted, **the efficacy of the claimed method for improving an immune response to a vaccine antigen has not even been established for mice model.** Based on *re-Wands* factors analysis disclosed above, the Examiner concluded that it would require undue experimentation to one skill in the art to practice the claimed invention.

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With regard to Declaration under U.S.R 1.132 by Dr. Boyd.

Declaration, Dr. Boyd discussed several additional data alleged to be provided in Exhibits A-D. It is noted, however, that there were no Exhibits A-D attached to said declaration, thus the Examiner can not comment on any of additional data.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of improving an immune response to a vaccine antigen by disrupting sex steroid mediated signaling through administering one or more pharmaceutical as claimed in claims 15, 30-33, 35, 36, 39-60, 63-68, 75 and 76 in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this

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application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 15, 30-33, 35, 36,39-60, 63-68, 75 and 76 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending US Applications:

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11/296676
10/748831
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10749122
10/553594
10/553608

While the instant and copending claims do differ in certain characteristics, the instant and copending claims appear to be drawn to the same or nearly the same method for reactivating the thymus of the patient by disruption of sex-mediated signaling to the thymus by administration of a pharmaceutical and administering HSC.

In the interest of compact prosecution, Applicant is invited to indicate whether or not the differences between the instant and each of the copending sets of claims are obvious as they read on method for improving an immune response to a vaccine antigen, comprising reactivating the thymus of the patient by disruption of sex-mediated signaling to the thymus by administration of a pharmaceutical and administering HSC

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant requests that said provisional rejection be held in abeyance until time as allowable subject matter is indicated in the instant application.

As has been discussed supra, the subject matter of the instant claims 15, 30-33, 35, 36,39-60, 63-68, 75 and 76 is currently not allowable.

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The following new grounds of rejection is necessitated by the amendment filed 10/13/06.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 41 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 41 and 42 contains the trademark/trade name LUPRON, METERELIN, CYSTORELIN, Aberelix, Cetrorelix, etc. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe LHRH agonists or pharmaceuticals and, accordingly, the identification/description is indefinite.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

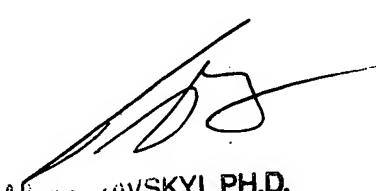
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskiy whose telephone number is 571/ 272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



MICHAEL BELYAVSKIY, PH.D.
PATENT EXAMINER

12/07/06